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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
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EXAMINER

FORMAN, B

ART UNIT	PAPER NUMBER
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1655

DATE MAILED:

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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.

09/335,218

Applicant(s)

WRIGHT ET AL.

Examiner

BJ Forman

Art Unit

1655

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☐ Responsive to communication(s) filed on 07 February 2001.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-24 and 55-62 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☐ Claim(s) 1-24 and 55-62 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are objected to by the Examiner.
- 11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved.
- 12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

- 13) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.
- 14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

- 15) ☐ Notice of References Cited (PTO-892)
- 16) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 17) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 9.
- 18) ☐ Interview Summary (PTO-413) Paper No(s) _____.
- 19) ☐ Notice of Informal Patent Application (PTO-152)
- 20) ☐ Other:

Art Unit: 1655

DETAILED ACTION

1. This action is in response to papers filed 7 February 2001 in Paper No. 10 in which claim 55 was amended and in response to Declaration under 37 C.F.R § 1.132 filed 13 February 2001 in Paper No. 11. The amendments have been thoroughly reviewed and entered. The previous rejections under 35 U.S.C. 102(e) and 35 U.S.C. 103(a) are maintained. All of the arguments have been thoroughly reviewed and are discussed below.

Currently claims 1-24 and 55-62 are under prosecution.

Claim Rejections - 35 USC § 102

2. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

3. Claims 1-5, 14-18 & 24 are rejected under 35 U.S.C. 102(e) as being anticipated by Schram et al. (U.S. Patent No. 5,681,705, filed 28 August 1995)

The applied reference has a common inventor with the instant application. Based upon the earlier effective U.S. filing date of the reference, it constitutes prior art under 35 U.S.C. 102(e). This rejection under 35 U.S.C. 102(e) might be overcome either by a showing under 37 CFR 1.132 that any invention disclosed but not claimed in the reference was derived from the inventor of this application and is thus not the invention "by another," or by an appropriate showing under 37 CFR 1.131.

Art Unit: 1655

Regarding Claim 1, Schram et al. disclose the method for detecting a target region having a single nucleotide difference (Column 4, lines 56-67 and Column 5, lines 1-5) in a target comprising hybridizing a detector primer i.e. SEQ ID NO: 1 and a second primer i.e. SEQ ID NO: 4 (Example 4, Column 10, lines 24-27 and Column 5, Table 1) to the target such that extension of the second primer by polymerase displaces the detector primer from the target sequence (Column 3, lines 53-58) wherein the detector primer comprises a diagnostic nucleotide for the single nucleotide difference which is a 3' terminal nucleotide or about one to four nucleotides from the 3' terminal nucleotide of the detector primer (Column 5, lines 18-27), extending the detector primer and the second primer with polymerase to produce a displaced detector primer extension product (Column 3, lines 56-59), determining the efficiency of detector primer extension (Column 7, lines 37-52), and detecting the presence or absence of the target region having the single nucleotide difference based on the efficiency of detector primer extension (Example 1, Column 8, Table 2 and Example 4, Column 10, lines 49-52). The method of Schram et al. includes an amplification step however, the open claim language "comprising" recited in the instant claim encompasses the addition of an amplification step.

Regarding Claim 2, Schram et al. disclose the method of Claim 1 wherein the single nucleotide difference is identified using the detector primer (Column 7, line 37-41).

Regarding Claim 3, Schram et al. disclose the method of Claim 2 wherein the single nucleotide difference is identified using multiple detector primers i.e. SEQ ID NO: 1 & 3 (Example 4, Column 10, lines 24-26) each comprising a different diagnostic nucleotide (Column 5, Table 1).

Regarding Claim 4, Schram et al. disclose the method of Claim 3 wherein two detector primers are used to identify which of two possible target sequences are present (Example 4, Column 10, lines 25-26 and Column 5, Table 1).

Regarding Claim 5, Schram et al. disclose the method of Claim 3 wherein four detector primers are used i.e. SEQ ID NO: 1, 3, 11 & 12 (Example 4, Column 10, lines 25 and 34-36)

Art Unit: 1655

wherein SEQ ID NO: 11 & 12 are detector probes extended in a primer extended in a primer extension assay (Column 10, lines 31-36).

Regarding Claim 14, Schram et al. teach the method of Claim 13 wherein the amplification reaction is selected from the group PCR, SDA and 3SR (Column 6, lines 49-53).

Regarding Claims 15-17, Schram et al. teach the method of Claim 1 wherein the detector primer is about 12-50, 12-24, and 12-19 nucleotides long (Column 5, Table 1).

Regarding Claim 18, Schram et al. teach the method of Claim 1 wherein the presence or absence of the single nucleotide difference is detected by means of a label associated with the detector primer (Column 7, lines 39-41).

Regarding Claim 24, Schram et al. teach the method of Claim 1 wherein the efficiency of detector primer extension is determined quantitatively (Example 1, Table 2 and Example 4, Column 10, lines 49-53).

Response to Arguments

4. Applicant argues that Schram et al. do not teach the diagnostic nucleotide is at the 3' terminus or within about 1-4 nucleotides of the 3' terminus as claimed. This argument is not found persuasive because Schram et al. teach "the 3' end of each SDA primer determines its target specificity" and the targets sequences (i.e. *M. avium* and *M. intracellulare*) "differ by a single nucleotide at each end of the target" (Column 5, lines 17-19). Therefore, the primers of Schram et al. comprise a target-specific (i.e. diagnostic) nucleotide at the 3' terminal nucleotide as claimed.

Response to Declaration under 37 C.F.R. § 1.132

5. Dr. Nadeau argues that the primers of Schram et al. (i.e. SEQ ID NO:1, 2 & 3) have a diagnostic nucleotide at 6 and 12 nucleotides from the 3' terminal and do not have a diagnostic nucleotide at the 3' terminus. This argument is not found persuasive because, as cited above, Schram et al. teach "the 3' end of each SDA primer determines its target specificity" and the targets sequences (i.e. *M. avium* and *M. intracellulare*) "differ by a single nucleotide at each end of the target" (Column 5, lines 17-22). Therefore, Schram et al. teach primers having a target-specific (i.e. diagnostic) nucleotide at the 3' terminal nucleotide as claimed. Dr. Nadeau notes

Art Unit: 1655

the figure accompanying the Declaration to illustrate hybridization of SEQ ID NO: 1 (Prim1) and SEQ ID NO: 2 (IN2B) to their target sequences and to further illustrate the 5' position of the diagnostic nucleotide. The figure is not found persuasive because SEQ ID NO: 1 and 2 of Schram et al. consist of 34 and 38 nucleotides respectively and not the 11 and 13 nucleotides illustrated. Additionally, INB2 does not align with SEQ ID NO: 2 or 3 as stated by Dr. Nadeau (page 1, last line-page 2, first paragraph)

Dr. Nadeau argues that proper placement of the diagnostic nucleotide is essential to achieve discrimination between target when using a single detector primer in a strand displacement reaction. However, it is noted that the instant invention is not drawn to a strand displacement reaction using a single detector primer. Therefore, this argument is not found persuasive because it is not drawn to the claimed invention.

Dr. Nadeau argues the results obtained when the diagnostic nucleotide was placed within about one to four nucleotides from the 3' terminus were unexpected based on known melting temperatures of DNA hybrids, because based on melting, a mismatch toward the center of the binding sequence would be expected to be more destabilizing than a mismatch near the terminus. Therefore, Dr. Nadeau argues, one would expect increasing specificity for the target as the diagnostic nucleotide is moved toward the center of the diagnostic primer. This argument is not found persuasive because it was well known in the art at the time the claimed invention was made that complementation between the template and the 3' nucleotide of the primer was essential for stabilized primer binding and subsequent primer extension (see Vary et al. al. U.S. Patent No. 4,851,331, filed 16 May 1986, Example 4).

Claim Rejections - 35 USC § 103

6. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Schram et al. in view of Walker et al.

Art Unit: 1655

7. Claims 6-13 are rejected under 35 U.S.C. 103(a) as being obvious over Schram et al. (U.S. Patent No. 5,681,705, filed 28 August 1995) as applied to Claim 1 above in view of Walker et al. (U.S. Patent No. 5,270,184, filed 19 November 1991).

Regarding Claim 6, Schram et al. teach the method of Claim 3 wherein each of the detector primers has a 5' restriction enzyme recognition sequence (Column 3, lines 34-36). Schram et al. do not teach each of the detector primers has a different 5' sequence. However, detector primers having a different 5' sequence i.e., methylated or unmethylated was known in the art as taught by Walker et al. (Column 10, lines 2-22 and 32-66). Therefore, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the claimed invention was made to modify the method of Schram et al. with the teaching of Walker et al. to obtain the claimed invention because the skilled practitioner in the art would have been motivated with a reasonable expectation of success to construct primers having a different 5' restriction enzyme recognition sequence for the expected benefit of specific and rapid isolation and identification of primer extension products.

Regarding Claim 7, Schram et al. teach the method of Claim 1 wherein the detector primer has a 5' non-diagnostic restriction enzyme recognition sequence but they do not teach the non-diagnostic sequence forms mismatch with the target sequence. However, primers having 5' non-diagnostic mismatch were known in the art as taught by Walker et al. (Column 8, lines 33-35 and Fig. 1, S1 and S2) who teach the 5' non-diagnostic mismatch is an enzyme recognition site. It would have been *prima facie* obvious to one of ordinary skill in the art to modify the method of Schram et al. with the teaching of Walker et al. to obtain the claimed invention because one skill in the art would have been motivated with a reasonable expectation of success to modify the restriction sequence of Schram et al. with the mismatched restriction sequence of Walker et al. for the expected benefit of producing quantities of amplified fragments having defined ends (Walker et al. , Column 4, lines 53-59).

Art Unit: 1655

Regarding Claims 8-10 Schram et al. teach the method of Claims 1 & 7 wherein the non-diagnostic nucleotide i.e. 5' restriction enzyme recognition sequence, GTTG is within 15 nucleotides i.e. adjacent to the diagnostic nucleotide (Column 5, Table 1). Schram et al. do not teach the recognition sequence is a mismatch and they do not teach the mismatch is 1-5 nucleotides from the diagnostic nucleotide. However, detector primers having a non-diagnostic mismatch within fifteen nucleotides of the diagnostic nucleotide were known in the art as taught by Walker et al. Specifically, Walker et al. teach the non-diagnostic mismatch i.e. 5' restriction enzyme recognition sequence is within 15 nucleotides of the diagnostic nucleotide wherein the primers are 20-100 nucleotides (Column 8, lines 27-28) and the enzyme recognition sequences are 5-19 nucleotides (Column 10, lines 30-66). It would have been *prima facie* obvious to one of ordinary skill in the art at the time the claimed invention was made to modify the primers of Schram et al. with the Walker et al. teaching to obtain the claimed invention because one of skill in the art would have been motivated with a reasonable expectation of success to apply the Walker et al. primers having the diagnostic nucleotide proximal to the enzyme-recognition mismatches to the method of Schram et al. for obvious benefit increased binding efficiency and reduced cost of primer synthesis.

Regarding Claim 11, Schram et al. teach the detector primers are 15-36 nucleotides long (Column 5, Table 1) and Walker et al. teach the detector primers are 15-36 nucleotides long (Column 8, line 30).

Regarding Claim 12, Schram et al. teach the detector primers are 18-24 nucleotides long (Column 5, Table 1) and Walker et al. teach the detector primers are 18-24 nucleotides long (Column 8, line 30).

Regarding Claim 13, Schram et al. teach the method of Claim 1 wherein the second primer is a bumper primer (Column 3, lines 53-56). Schram et al. do not teach the second primer is an amplification primer. However, extension primers were routinely used in the art as amplification primers wherein the first step in amplification is primer extension. Therefore,

Art Unit: 1655

it would have been *prima facie* obvious to one of ordinary skill in the time the claimed invention was made that amplification primers were also extension primers.

Schram et al. in view of Walker et al.

8. Claims 19-21 are rejected under 35 U.S.C. 103(a) as being obvious over Schram et al. (U.S. Patent No. 5,681,705, filed 28 August 1995) as applied to Claim 18 above in view of Walker et al. (U.S. Patent No. 5,270,184, filed 19 November 1991).

Regarding Claim 19, Schram et al. teach the method of Claim 18, but they do not teach the label produces a change in signal upon extension of the primer. However, Walker et al. teach a similar method for detecting a target sequence using detector primer extension wherein a label produces a change in signal upon extension of the detector primer i.e. fluorescence polarization (Column 12, lines 51-55).

Regarding Claim 20, Schram et al. teach the method of Claim 18, but they do not teach the label is a fluorescent donor/quencher dye. However, Walker et al. teach a similar method for detecting a target sequence wherein the label is a fluorescent donor/quencher i.e. fluorescence energy transfer (Column 12, lines 51-57).

Regarding Claim 21, Schram et al. teach the method of Claim 18, but they do not teach the label produces a change in signal upon extension of the primer. However, Walker et al. teach a similar method for detecting a target sequence using detector primer extension wherein a label produces a change in signal upon extension of the detector primer i.e. fluorescence polarization (Column 12, lines 51-55).

Schram et al. in view of Thomas et al.

9. Claims 22 & 23 are rejected under 35 U.S.C. 103(a) as being unpatentable over Schram et al. (U.S. Patent No. 5,681,705, filed 28 August 1995) as applied to claim 1 above, and further in view of Thomas et al. (U.S. Patent No. 6,025,130, filed 23 May 1996). Schram et

Art Unit: 1655

al teach the method of Claim 1 wherein a single nucleotide difference is detected in a target sequence. Schram et al do not teach the method wherein a single nucleotide difference in the HFE gene is detected. However, the HFE i.e. Hereditary Hemochromatosis (HH) was known to have a single nucleotide difference i.e. mutation in exon 4 as taught by Thomas et al. (Column 16, lines 25-33). Thomas et al. teach a single nucleotide difference in exon 4 i.e. 24d1 wherein the mutation is responsible for the majority of hereditary hemochromatosis (Column 11, lines 63-64) and they teach primers for target-specific amplification and detection of the 24d1 mutation (Column 17, lines 1-4 and Fig 6A). Therefore, it would have been *prima facie* obvious to one of ordinary skill in the art to modify the method of Schram et al. with the teaching of Thomas et al. to obtain the claimed invention because one skilled in the art would have been motivated with a reasonable expectation of success to apply the target-specific amplification method of Schram et al. to the primer and target sequences taught by Thomas et al. for the expected benefit of efficient diagnosis of disease-causing mutations.

Vary et al. in view of Schram et al. and Walker et al.

10. Claims 1-21, 24 & 55-62 are rejected under 35 U.S.C. 103(a) as being unpatentable over Vary et al. (U.S. Patent No. 4,851,331, filed 16 May 1986) in view of Schram et al. (U.S. Patent No. 5681,705, filed 28 August 1995) and Walker et al. (U.S. Patent No. 5,270,184, filed 19 November 1991).

Regarding Claim 1, Vary et al. disclose the method for detecting a single nucleotide difference in a target (Column 1, lines 47-50 and Column 2, lines 35-38 and Example 3) comprising hybridizing a detector primer wherein the detector primer comprises a diagnostic nucleotide for the single nucleotide difference which is the 3' terminal nucleotides of the detector primer (Column 1, lines 57-65 and Example 3, Column 12, lines 21-22), extending the detector primer with polymerase to produce a detector primer extension product (Column 1, lines 65-68 and Example 3, Column 12, lines 26-50), determining the efficiency of detector

Art Unit: 1655

primer extension (Column 12, lines 52-68 and Table 5), and detecting the presence or absence of the single nucleotide difference based on the efficiency of detector primer extension (Example 3, Column 12, lines 57-60 and Table 5). Vary et al. teach the method for detecting a single nucleotide difference but they do not teach the method wherein the primer extension product is displaced by extension of a second primer. However, displacement of primer extension product i.e. strand displacement was known in the art as taught by Schram et al. who teach a similar method for detecting a single nucleotide difference wherein the primer extension is dissociated from the template by extension of an upstream primer (Column 3, lines 61-64). It would have been *prima facie* obvious to one of ordinary skill in the art to modify the Vary et al. method with the teaching of Schram et al. to obtain the claimed invention because one of skill in the art would have been motivated with a reasonable expectation of success to apply the strand displacement teaching of Schram et al. to the method of Vary et al. for the obvious benefit of producing a quantity of extension product.

Regarding Claim 2, Vary et al. disclose the method of Claim 1 wherein the single nucleotide difference is identified by labeled primer extension product (Example 3, Column 12, lines 55-60 and Table 5). Vary et al. do not teach identification using the detector primer. However, primer labeling was routinely practiced in the art at the time the claimed invention was made as an alternative to incorporation of label into the primer extension product. It would have been *prima facie* obvious to one of skill in the art to modify the method of Vary et al. and label the primer because the skilled practitioner would have been motivated with a reasonable expectation of success to use labeled primers based on the commercial availability of labeled primers and desired results.

Regarding Claim 3, Vary et al. disclose the method of Claim 2 wherein the single nucleotide difference is identified using multiple detector primers each comprising a different diagnostic nucleotide (Example 3, Column 12, lines 21-25).

Art Unit: 1655

Regarding Claim 4, Vary et al. disclose the method of Claim 3 wherein two detector primers are used to identify which of two possible target sequences are present (Example 4, Column 13).

Regarding Claim 5, Vary et al. do not disclose the method of Claim 3 wherein four detector primers are used. However, multiple detector primers were known in the art as taught by Schram et al. who teach similar method for detecting a single nucleotide difference wherein four detector primers are used i.e. SEQ ID NO: 1, 3, 11 & 12 (Example 4, Column 10, lines 25 and 34-36). It would have been *prime facie* obvious to one of skill in the art to modify the method of Vary et al. with the teaching of Schram et al. to obtain the claimed invention because the skilled practitioner in the art would have been motivated with a reasonable expectation of success to apply the multiple detector primer teaching of Schram et al. to the method of Vary et al. for the expected benefit of specifically identifying multiple species in a complex sample.

Regarding Claim 6, Vary et al. teach the method of Claim 3 wherein each of the detector primers have a specific 5' recognition sequence (Column 7, lines 26-30 and Fig. 3) and they teach numerous 5' tails. Vary et al. do not teach each of the detector primers has a different 5' sequence. However, it would have been *prima facie* obvious to one of ordinary skill in the art modify the primers of Vary et al. with the teaching of Vary et al. to obtain the claimed invention because one of skill in the art would have been motivated with a reasonable expectation of success to apply the teaching of Vary et al. to construct primers wherein each has a different 5' sequence for the expected benefit of specific and rapid isolation and identification of primer extension products.

Regarding Claim 7, Vary et al. teach the method of Claim 1 wherein the detector primer has a 5' non-diagnostic recognition sequence which forma non-diagnostic mismatch with the target sequence (Column 7, lines 26-30 and Fig. 3)

Art Unit: 1655

Regarding Claims 8-10 Vary et al. teach the method of Claim 1 wherein the non-diagnostic nucleotide is within 15 nucleotides i.e. adjacent to the diagnostic nucleotide. Specifically, Vary et al. teach the detector primes are 10 nucleotides in length (Column 2, lines 52-23) having a 5' non-diagnostic mismatch and a 3' diagnostic nucleotide (Column 7, lines 24-28). Therefore, it would have been *prima facie* obvious to one of ordinary skill in the art that the non-diagnostic nucleotides and the diagnostic nucleotide are within 15 nucleotides, positioned 1-5 nucleotides apart, and/or adjacent and the skilled practitioner would have been motivated with a reasonable expectation of success to construct primers having defined 5' to 3' proximity based on the size of the target region and for known benefit of synthesizing smaller primers chemically as taught by Vary et al. (Column 2, lines 52-54).

Regarding Claims 11 & 12, Vary et al. teach the detector primers are 15-36 nucleotides long and 18-24 nucleotides long (Column 2, lines 52-53).

Regarding Claim 13, Vary et al. teach the method of Claim 1 wherein the second primer is an extension primer (Example 3, Column 12, lines 20-22). Vary et al. do not teach the second primer is an amplification primer. However, extension primers were routinely used in the art as amplification primers wherein the first step in amplification is primer extension. Therefore, it would have been *prima facie* obvious to one of ordinary skill in the time the claimed invention was made that amplification primers were also extension primers.

Regarding Claim 14, Vary et al. teach the method of Claim 13 wherein the extension reaction is performed in the presence of AMV Reverse Transcriptase (Example 3). However, Schram et al. teach a similar method for detecting a single nucleotide difference wherein the detection method includes an amplification reaction i.e. SDA (Column 4, line 67 through Column 5, lines 1-5). It would have been *prime facie* obvious to one of ordinary skill in the art at the time the claimed invention was made to modify the method of Vary et al. with the SDA teaching of Schram et al. to obtain the claimed invention because one of skill in the art would have been motivated with a reasonable expectation of success to apply SDA to the method of

Art Unit: 1655

Vary et al. for the expected benefit of species-specific target region detection as taught by Schram et al. (Column 4, lines 48-50)

Regarding Claims 15-17, Vary et al. teach the method of Claim 1 wherein the detector primer is about 12-50, 12-24, and 12-19 nucleotides long (Column 2, lines 52-53).

Regarding Claim 18, Vary et al. teach the method of Claim 1 wherein the presence or absence of the single nucleotide difference is detected by means of a label associated with the detector primer (Example 2, Column 11, lines 60-62) wherein the label is associated with the detector primer by virtue of the primer extension product.

Regarding Claim 19, Vary et al. teach the method of Claim 18 wherein the label becomes detectable upon extension of the primer due to the incorporation of labeled nucleotides (Column 3, lines 54-59, Fig 1E and Fig 4F)

Regarding Claim 20, Vary et al. teach the method of Claim 18, but they do not teach the label is a fluorescent donor/quencher dye. However, Walker et al. teach a similar method for detecting a single nucleotide difference in a target sequence by detection of the detector primer extension wherein the label is a fluorescent donor/quencher i.e. fluorescence energy transfer (Column 12, lines 51-57).

Regarding Claim 21, Vary et al. teach the method of Claim 18, but they do not teach the label produces a change in signal upon extension of the primer. However, Walker et al. teach a the method for detection of the detector primer extension wherein a label produces a change in signal upon extension of the detector primer i.e. fluorescence polarization (Column 12, lines 51-55).

Regarding Claim 24, Vary et al. teach the method of Claim 1 wherein the efficiency of the detector primer extension is determined quantitatively (Example 3, Table 5). Specifically, Vary et al. teach the efficiency of detector primer extension is determined quantitatively by measuring the incorporation of labeled nucleotide into the extension product (Example 3, Table 5) and wherein the efficiency incorporation was dependent upon complementation between the

Art Unit: 1655

3' nucleotide of the primer and the template (Example 4, Column 13, lines 56-68 and Column 14, lines 1-4).

Regarding Claim 55, Vary et al. teach the method for detecting a single nucleotide difference in a target sequence (Column 1, lines 47-50 and Column 2, lines 35-38 and Example 3) comprising hybridizing to the target sequence a detector primer comprising a diagnostic nucleotide for the single nucleotide difference which is a 3' terminal nucleotide of the detector primer (Column 1, lines 57-65 and Example 3, Column 12, lines 21-22), extending the detector primer with polymerase to produce a detector primer extension product (Column 1, lines 65-68 and Example 3, Column 12, lines 26-50), and detecting the presence or absence of the single nucleotide difference based on the efficiency of detector primer extension (Example 3, Column 12, lines 57-60 and Table 5). Vary et al. teach the method for detecting a single nucleotide difference but they do not teach the method wherein the primer extension product is displaced by extension of a second primer. However, displacement of primer extension product i.e. strand displacement was known in the art as taught by Schram et al. who teach a similar method for detecting a single nucleotide difference wherein the primer extension is dissociated from the template by extension of an upstream primer (Column 3, lines 61-64). It would have been *prima facie* obvious to one of ordinary skill in the art to modify the Vary et al. method with the teaching of Schram et al. to obtain the claimed invention because one of skill in the art would have been motivated with a reasonable expectation of success to apply the strand displacement teaching of Schram et al. to the method of Vary et al. for the expected benefit of producing extension products which can be amplified taught by Schram et al. (Column 3, lines 53-54).

Regarding Claim 56, Vary et al. do not teach the single nucleotide polymorphism is identified using the detector primer. However, Schram et al. teach a similar method for detecting a single nucleotide difference wherein the difference is identified using the detector primer (Column 7, line 37-41).

Art Unit: 1655

Regarding Claim 57, Vary et al. teach the method wherein the single nucleotide difference is identified using multiple detector primer each comprising a different diagnostic nucleotide (Column 12, lines 21-25) and Schram et al. teach the method wherein the single nucleotide difference is identified using multiple detector primers i.e. SEQ ID NO: 1 & 3 (Example 4, Column 10, lines 24-26) each comprising a different diagnostic nucleotide (Column 5, Table 1).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the claimed invention was made to modify the method of Vary et al. with the teachings of Schram et al. to obtain the claimed invention because the skilled practitioner in the art would have been motivated with a reasonable expectation of success to modify the detection of Vary et al. with the detector primer and multiple detector primers of Schram et al. for the obvious benefit of specifically detecting diagnostic component.

Regarding Claim 58, Vary et al. teach the method of Claim 3 wherein each of the detector primers have a specific 5' recognition sequence (Column 7, lines 26-30 and Fig. 3) and they teach numerous 5' tails. Vary et al. do not teach each of the detector primers has a different 5' sequence. However, detector primers having a different 5' sequence i.e. methylated or unmethylated was known in the art as taught by Walker et al. (Column 10, lines 2-22 and 32-66). It would have been *prima facie* obvious to one of ordinary skill in the art at the time the claimed invention was made to modify the method of Vary et al. with the teaching of Walker et al. to obtain the claimed invention because the skilled practitioner in the art would have been motivated with a reasonable expectation of success to construct primers having a different 5' restriction enzyme recognition sequence for the expected benefit of specific and rapid isolation and identification of primer extension products.

Regarding Claim 59, Schram et al. teach the method of Claim 1 wherein the second primer is a bumper primer (Column 3, lines 53-56). Schram et al. do not teach the second primer is an amplification primer. However, extension primers were routinely used in the art

Art Unit: 1655

as amplification primers wherein the first step in amplification is primer extension. Therefore, it would have been *prima facie* obvious to one of ordinary skill in the time the claimed invention was made to modify the method of Vary et al. with the bumper primer of Schram et al. for extension and amplification.

Regarding Claim 60, Vary et al. teach the method of Claim 55 wherein the label becomes detectable upon extension of the primer due to the incorporation of labeled nucleotides (Column 3, lines 54-59, Fig 1E and Fig 4F)

Regarding Claim 61, Vary et al. teach the method of Claim 55, but they do not teach the label is a fluorescent donor/quencher dye. However, Walker et al. teach a similar method for detecting a single nucleotide difference in a target sequence by detection of the detector primer extension wherein the label is a fluorescent donor/quencher i.e. fluorescence energy transfer (Column 12, lines 51-57). It would have been *prima facie* obvious to one of ordinary skill in the art at the time the claimed invention was made to modify the method of Vary et al. with the teachings of Walker et al. to obtain the claimed invention because the skilled practitioner in the art would have been motivated with a reasonable expectation of success to modify the label of Vary with the donor/quencher of Walker et al. for the known benefit of simple and convenient detection without product isolation as taught by Walker et al. (Column 12, lines 49-50).

Regarding Claim 62, Vary et al. teach the method wherein the diagnostic nucleotide is a 3' terminal nucleotide (Column 8, lines 5-61).

Vary et al. and Schram et al. in view of Thomas et al.

11. Claims 22 & 23 are rejected under 35 U.S.C. 103(a) as being unpatentable over Vary et al. (U.S. Patent No. 4,851,331, filed 16 May 1986) and Schram et al. (U.S. Patent No. 5,681,705, filed 28 August 1995) as applied to claim 1 above, and further in view of Thomas et al. (U.S. Patent No. 6,025,130, filed 23 May 1996). Vary et al. and Schram et al. teach the method of Claim 1 wherein a single nucleotide difference is detected in a target sequence. Vary

Art Unit: 1655

et al. and Schram et al do not teach the method wherein a single nucleotide difference in the HFE gene is detected. However, the HFE i.e. Hereditary Hemochromatosis gene (HH) was known to have a single nucleotide difference in exon 4 as taught by Thomas et al. (Column 11, lines 56-59 and Column 16, lines 59-65). Thomas et al. teach a single nucleotide difference i.e. mutation in exon 4 of the HH gene i.e. 24d1 (Column 16, lines 25-33) wherein the difference is responsible for the majority of hereditary hemochromatosis (Column 11, lines 63-64) and they teach primers for target-specific detection of the 24d1 difference (Column 17, lines 1-4 Fig 6A). Therefore, it would have been *prima facie* obvious to one of ordinary skill in the art to modify the method of Vary et al. and Schram et al. with the teaching of Thomas et al. to obtain the claimed invention because one skilled in the art would have been motivated with a reasonable expectation of success to apply the target-specific detection method of Vary et al. and Schram et al. to the primer and target sequences taught by Thomas et al. for the expected benefit of efficient gene-based diagnosis of disease-causing mutation.

Response to Arguments

12. Applicant cites the Declaration by Dr. Nadeau wherein it is acknowledged that Schram et al. were able to distinguish single nucleotide polymorphism (SNP) using primers containing diagnostic nucleotides. However, applicant argues that Schram et al. are unable to distinguish a SNP when a single detector primer containing a diagnostic nucleotide at the -12 position was employed. The argument is not found persuasive because as stated above in ¶ 4, Schram et al. clearly teach the diagnostic nucleotide at the 3' terminus i.e. "the target binding sequence at the 3' end of each SDA primer determines its target specificity" (Column 5, lines 17-19). Additionally, in response to applicant's argument that the references fail to show certain features of applicant's invention, it is noted that the features upon which applicant relies (i.e., single detector primer) are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993). Additionally, the open claim language "comprising" recited in the instant claims encompasses additional primers taught by Schram et al.

Applicant further argues that there is no suggestion in the Vary et al. reference that would solve the problem encountered by Schram et al. and therefore, there is no suggestion to apply the teaching of Vary et al. to the method of Schram. In response to applicant's argument

Art Unit: 1655

that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988) and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In the instant case, Schram et al. teach a detector primer having a diagnostic nucleotide at the 3' end for use in strand displacement reactions for detecting a single nucleotide difference efficiently (Column 4, lines 56-61) and Vary et al. teach detector primers having a diagnostic nucleotide at the 3' end for detecting a single nucleotide difference (Column 2, lines 57-68) and one skilled in the art would have been motivated to apply the 3' detector primers of Vary et al. to 3' detector primers and the strand displacement taught by Schram et al. for the expected benefit of efficient and specific single-nucleotide detection as taught by Vary et al. (Column 2, lines 35-38) and Schram et al. (Column 4, lines 56-61).

Response to Declaration under 37 C.F.R. § 1.132

13. The response to Dr. Nadeau arguments regarding the Schram et al. patent are discussed above in ¶ 5.

With regard to the Vary et al. reference, Dr. Nadeau argues that although Vary et al. teach a primer having a 3' terminal mismatch for detection of sequence variations, they do not teach the primer in a strand displacement reaction and Dr. Nadeau further argues that neither the Schram et al. or Vary et al. patent suggest using the primer of Vary et al. in the method of Schram et al. This argument is not found persuasive because as stated above, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988) and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). However, one skilled in the art would have been motivated to apply the 3' detector primers of Vary et al. to 3' detector primers and the strand displacement taught by Schram et al. for the expected benefit of efficient and specific single-nucleotide detection as taught by Vary et al. (Column 2, lines 35-38) and Schram et al. (Column 4, lines 56-61).

Art Unit: 1655

Double Patenting

14. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

15. Claims 1-8, 11, 12, 15-18 & 24 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 3, 7, 10 & 13 of U.S. Patent No. 5,681,705 filed 28 August 1995. Although the claims are not identical, they are not patentably distinct because both sets of claims are drawn to a method for detecting a single nucleotide difference in a target sequence using detector primers having 3' specificity for the target regions wherein the nucleotide difference is detected by extension of the detector primers. The only difference between the claim sets is that the patent claims recite an amplification step in the method wherein amplification results in loss of the originally present mismatch (Column 6, lines 8-15). It would have been *prime facie* obvious to one of ordinary skill in the art to modify the patent method and to omit the amplification step wherein the function is not desired or required based on the obvious benefit of reducing time, labor and material costs. The courts have stated that it would be obvious to omit an element when a function attributed to said element is not desired or required (see *Ex parte Wu*, 10 USPQ 2031).

16. Claims 1-8, 11-18 & 24 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 3, 7, 10 & 13 of U.S. Patent No. 5,681,705, filed 28 August 1995. Although the claims are not identical, they are not patentably distinct because both sets of claims are drawn to a method for detecting a single

Art Unit: 1655

nucleotide difference in a target sequence using detector primers having 3' specificity for the target regions. The only difference is the patent claims recite amplification primers consisting of SEQ ID NO: 1, 2, 3 and the application claims recite detector primers. However, the patent defines the amplification primers contain a 3' single nucleotide which discriminates between perfect match and mismatch primer-target binding (Column 5, lines 17-34). Similarly, the application defines the detector primers contain a 3' nucleotide which discriminates between perfect match and mismatch primer-target binding (page 4, lines 2-7). Therefore, it would have been *prima facie* obvious to one of skill in the art to apply the patent primer teaching to the patent method to obtain the claimed invention for the expected benefit of universal detection of single nucleotide differences.

Response to Arguments

17. Applicant argues that the patent claims are drawn to SEQ ID NO: 1, 2 & 3 which do not have a mismatch in the instantly claimed position and it would not have been obvious to move the mismatch position to the claimed position. This argument is not found persuasive because as stated above in ¶ 5, Schram et al. teach the primer comprises a 3' terminal nucleotide which is diagnostic (Column 5, lines 17-22). Applicant further argues that the examiner's reference to the '705 patent teaching of a diagnostic nucleotide at the 3' terminus is incorrect because the disclosure refers only to the position of the target binding sequence of the primer and not the diagnostic nucleotide. This argument is not found persuasive because as stated above, Schram et al. teach the target binding sequence is diagnostic i.e. "determines target specificity" (Column 5, lines 17-19) wherein the "3' end of an SDA amplification primer (target binding sequence) hybridizes at the 3' end of the target sequence" (Column 3, lines 31-33) and wherein a single nucleotide difference is detected (Column 4, lines 56-67).

18. All claims are drawn to the same invention claimed in the application prior to the entry of the submission under 37 CFR 1.114 and could have been finally rejected on the grounds and art of record in the next Office action if they had been entered in the application prior to entry under 37 CFR 1.114. Accordingly, **THIS ACTION IS MADE FINAL** even though it is a

Art Unit: 1655

first action after the filing of a request for continued examination and the submission under 37 CFR 1.114. See MPEP § 706.07(b). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.


Conclusion

19. No claim is allowed.

20. Any inquiry concerning this communication or earlier communications from the examiner should be directed to BJ Forman whose telephone number is (703) 306-5878. The examiner can normally be reached on 6:45 TO 4:15.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Jones can be reached on (703) 308-1152. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-4242 for regular communications and (703) 308-8742 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.


BJ Forman, Ph.D.
February 22, 2001

